REMARKS

The Office Action of February 5, 2003 has been carefully considered and the following response prepared. Claims 1 and 13 have been amended. Claims 2 and 5 have been canceled without prejudice, and claims 3, 4, 6, and 8 have been amended to change their dependency to claim 1 in view of the cancellation of claims 2 and 5.

Claims 1-8 and 1-13 were rejected under 35 USC 112, second paragraph as indefinite.

Claim 1 has been amended to delete 4-hydroxypyruvate and replace it with 4-hydroxyphenylpyruvate. Support for this amendment can be found in the specification at page 1, line 22 and page 2, lines 15-25. No new matter has been added.

Claim 1 was also rejected as confusing in the recitation of a "first suitable enzyme" and a "second suitable enzyme", and claims 2 and 4 were objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. It appears that claim 4 was incorrectly mentioned in the rejection because it does not refer to a suitable HPA-hydroxylase. Claim 5 refers to a suitable HPA-hydroxylase.

Claims 2 and 5 have been canceled without prejudice. Claim 1 has been amended to incorporate the limitations of claims 2 and 5. Claim 1 now states that the first suitable enzyme is a suitable HPP-oxidase and that the second suitable enzyme is a suitable HPA-hydroxylase.

Claim 1 was further rejected as vague and indefinite for the recitation of "in the presence of a ... HPPD inhibitor" because the Examiner doubted that in the "presence" of large amounts of any inhibitor the reaction would succeed. The Examiner recommended that the inhibitor and enzymes used as well as the amounts thereof be better defined.

Applicants respectfully submit that the foregoing phrase is not vague and indefinite, nor is the description of the enzymes used vague and indefinite. The amount of HPPD inhibitor that would be used in the methods of the invention would vary depending on the particular HPPD inhibitor used, and persons skilled in the art can readily determine how much can be used. For example, persons skilled in the art could

refer to U.S. patent 6,268,549, and the published patent applications referred to therein, which disclose isoxazole, diketonitrile and sulcotrione HPPD inhibitors for guidance.

Further, the claims are not rendered indefinite without recitation of the amounts of enzyme used. The amount of enzyme used in the method will vary depending on factors such as the quantity of starting material to be converted, and persons skilled in the art can readily determine the quantity to be used.

Claim 1 was further rejected as confusing in the recitation of "said method is carried out" because the Examiner asserted the antecedent basis is unclear.

Claim 1 has been amended to state that the "enzymatic reactions" are carried out in the presence of a HPPD inhibitor. The antecedent basis for this amendment can be found in the third line of claim 1.

Claim 12 was objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to limit the subject matter of a previous claim. This objection is connected with the rejection of claim 1 as confusing on the basis that it cannot be readily ascertained whether the inhibitor is present in a one pot reaction or whether the inhibitor is added to one or both of two separate reactions in two separate vessels.

Applicants respectfully submit that claim 1 is not confusing or indefinite with respect to the location of the steps of the method. The method of claim 1 can be carried out in one reaction vessel or two separate reaction vessels; i.e., each enzymatic conversion in a separate reaction vessel. The HPPD inhibitor is present in the reaction medium during both enzymatic reactions in the reaction vessel or both reaction vessels if two are used. Claim 12 is drawn to the embodiment of claim 1 wherein the two suitable enzymes are present together at the same time in the reaction medium, thus referring to the first alternative where the method is carried out in one reaction vessel.

Claim 13 was rejected as vague and indefinite in the recitation "or alternatively they can be produced *in situ* by suitable biological organisms." The Examiner suggested substituting "are produced" for "can be produced". The Examiner also indicated that the phrase "biological organisms" appears redundant, and from the context of a "suitable reaction medium", it appears that the proper term should be "suitable microorganisms", since organisms such as animals appear excluded by the claims.

Claim 13 has been amended as suggested by the Examiner to substitute "are produced" for "can be produced". Applicants respectfully submit, however, that the term "biological organisms" is not redundant. The specification at page 4, lines 18-19 explain that the biological organism can be a bacterium, a yeast or a plant cell.

what others are there?

In view of the above, withdrawal of this section 112, second paragraph rejection is requested.

Claims 1-8 and 12-13 were rejected under 35 USC 103 as being *prima facie* unpatentable over Suemori et al. (1995) taken with Blakley et al., Suemori et al. (1996) and Hareland et al. The basis for the rejection is that it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the process of Suemori et al. (1995) by using further enzymes from other microorganisms for the bioconversion of HPP into HPA and the enzymatic bioconversion of HPA into HMO, in the presence of an HPPD inhibitor for the expected benefits of maximizing the yield of this valuable compound useful in a variety of pharmaceutical and industrial applications.

Applicants traverse this rejection. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the Applicant. The cited references, by themselves, must teach or suggest the claimed invention and provide the motivation to combine the references in the manner necessary to produce the claimed invention. It is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's disclosure as a template and selecting elements from references to fill the gaps.

The present rejection does not establish a *prima facie* case of obviousness.

Suemori *et al.* (1995) discloses studies on the degradation of tyrosine in *R. erythropolis* where the authors concluded that tyrosine was degraded through HPP and HPA to HMO. This publication discloses that HPA-hydroxylase catalyzes the reaction of HPA to HMO, but does not disclose any enzyme that catalyzes the conversion of HPP to HPA. Suemori *et al.* makes no suggestion whatever about the possibility or desirability of substituting enzymes from other microorganisms for the ones in *R. erythropolis* to produce HMO.

Suemori *et al.* (1996), Hareland *et al.* and Blakley *et al.* do not supply what is missing from Suemori *et al.*

Suemori *et al.* (1996) discloses purification and characterization of a HPA hydroxylase from the bacterium *R. erythropolis*, which is the same bacterium used by Suemori *et al.* (1995) and is hence not from a different microorganism. Moreover, there is no suggestion in Suemori *et al.* (1996) of combining enzymes from other microorganisms to produce HMO. Additionally, this publication, like Suemori et al. (1995) also fails to disclose any enzyme responsible for the bioconversion of HPP to HPA.

Hareland *et al.* discloses HPA-hydroxylase from *Pseudomonas acidovarans*, but does not make any suggestion whatever about the possibility or desirability of substituting enzymes from other microorganisms to produce HMO. The Examiner indicated that Hareland et al. discusses HPP-oxidase inhibitors at page 279, Figure 7 and that some activity remains in every instance, even though relatively high concentrations of inhibitor are used. Figure 7 Hareland et al. shows a graph of competitive inhibition of HPA-hydroxylase by various concentrations of 4-hydroxy-3-methylphenylacetic acid. Hareland et al. discloses HPA-hydroxylase inhibitors (page 278-279), not HPPD inhibitors as required by Applicants' claimed method. As none of these compounds are disclosed as inhibitors of HPPD, the inhibitors of HPA-hydroxylase would not have been taken into account by persons skilled in the art for a method conducted in the presence of an HPPD inhibitor.

Blakley et al. discloses experiments on the catabolism of L-tyrosine by an *Arthrobacter* species. The publication discloses that the *Arthrobacter* species metabolizes L-tyrosine by a pathway involving 3,4-dihydroxyphenylacetate (homoprotocachuate) as a key intermediate. Blakley et al. further states on page 1128 that the major pathway for the catabolism of L-tyrosine in mammals and probably microorganisms involves homogentisate as a key intermediate. Blakley et al. discloses HPP-oxidase from the *Athrobacter* species used in their experiments, but there is no suggestion whatever about the possibility or desirability of substituting enzymes from other microorganisms to produce HMO. The pathway disclosed in this publication

produces a different compound, 3,4-dihydroxyphenylacetate, whereas the claims of the present application are directed to methods of producing HMO.

The combination of Suemori *et al.* (1995) with Suemori *et al.* (1996), Hareland *et al.* and Blakley *et al.* amounts to an impermissible hindsight reconstruction of the claimed invention from isolated disclosures in the prior art. There is nothing in the cited references, alone or in combination, that suggest Applicants' claimed method of producing HMO by enzymatic means. Suemori et al. (1995) discloses HPA-hydroxylase, one of the enzymes used in the claimed method, but does not disclose HPP-oxidase, the other enzyme used in the claimed method. Similarly, Suemori et al. (1996) and Hareland et al. disclose HPA-hydroxylase but not HPP-oxidase. None of these references disclose or suggest combining enzymes from other microorganisms to produce HMO. Blakley et al. discloses HPP-oxidase, but this publication discloses a different pathway than Suemori et al. (1995) for catabolism of L-tryosine. Persons skilled in the art would not be motivated to look to this publication for an element of the claimed invention because it does not deal with the preparation of HMO.

The motivation for combining the cited references provided by the Examiner in the present rejection indicated that persons skilled the art would seek to combine the teachings of the cited references for the expected benefits of maximizing the yield of HMO which is useful in a variety of pharmaceutical and industrial applications.

The case *In re Sang-Su Lee,* 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002) explains the type of explanation and reasoning that is required to establish a *prima facie* case of obviousness and emphasizes that Examiners must clearly explain how and why the teachings of the cited references provide the motivation to combine the references in the manner necessary to support the obviousness rejection. The Federal Circuit has made it very clear that Examiners cannot rely on conclusory statements, such as those used in the present Office Action to establish the motivation to combine references.

In view of the above, Applicants submit that the Examiner has not established a *prima facie* case of obviousness. Withdrawal of this section 103 rejection is respectfully requested.

In view of the above, the present application is believed to be in a condition for allowance. Reconsideration of the application is requested and an early Notice of Allowance is earnestly solicited.

Respectfully submitted,
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